

In the Claims

1. (Currently Amended) A method for detecting, preventing, and/or treating a condition requiring regulation of trophoblast invasion comprising modulating ~~TGF $\beta$ <sub>3</sub>, receptors of cytokines of the TGF $\beta$  family,~~ HIF-1 $\alpha$ , or oxygen tension.

9. 2. (Currently Amended) A method for diagnosing in a subject a condition requiring regulation of trophoblast invasion comprising detecting ~~TGF- $\beta$ <sub>3</sub>, receptors of cytokines of the TGF $\beta$  family,~~ or HIF-1 $\alpha$  in a sample from the subject.

3. (Original) A method for diagnosing increased risk of preeclampsia in a subject comprising detecting TGF- $\beta$ <sub>3</sub> in a sample from the subject.

4. (Original) A method as claimed in claim 3 which comprises (a) collecting a sample from the subject; (b) measuring the levels of TGF- $\beta$ <sub>3</sub> in the sample; and (c) comparing the levels of TGF- $\beta$ <sub>3</sub> in the sample to the levels in women with normal pregnancies.

5. (Original) A method as claimed in claim 4 wherein the levels of TGF- $\beta$ <sub>3</sub> are measured in a sample from the subject during the first trimester of pregnancy.

6. (Original) A method of regulating trophoblast invasion comprising inhibiting or stimulating TGF- $\beta_3$ , receptors of cytokines of the TGF- $\beta$  family, HIF-1 $\alpha$ , or oxygen tension.

7. (Original) A method for increasing trophoblast invasion in a subject comprising administering an effective amount of an inhibitor of (a) TGF- $\beta_3$ , (b) receptors of cytokines of the TGF- $\beta$  family, or (c) HIF-1 $\alpha$ .

8. (Original) A method as claimed in claim 7 wherein the inhibitor is antisense to TGF- $\beta_3$ , or antisense to HIF-1 $\alpha$ .

9. (Original) A method as claimed in claim 7 wherein the inhibitor is an antibody to TGF- $\beta_3$ .

10. (Original) A method as claimed in claim 7 wherein the inhibitor is decorin, fetuin,  $\alpha_2$ -macroglobulin, or thyroglobulin, or peptides derived from sites on the compounds that bind to TGF- $\beta_3$ .

11. (Original) A method for reducing trophoblast invasion in a subject comprising administering an effective amount of (a) TGF- $\beta_3$ , (b) receptors of cytokines of the TGF- $\beta$  family, (c) HIF-1 $\alpha$ , or (d) a stimulator of (a), (b), or (c).

12. (Original) A method for treating a woman suffering from, or who may be susceptible to preeclampsia comprising administering therapeutically effective dosages of an inhibitor of (a) TGF- $\beta_3$ , (b) receptors of cytokines of the TGF- $\beta$  family, or (c) HIF-1 $\alpha$ .

13. (Original) A method for monitoring or treating choriocarcinoma in a subject comprising administering therapeutically effective dosages of (a) TGF- $\beta_3$ , (b) a receptor of cytokines of the TGF- $\beta$  family, (c) HIF-1 $\alpha$  and/or (d) stimulators of (a), (b) or (c).

14. (Original) A method for evaluating a compound for its ability to regulate trophoblast invasion comprising the steps of :

(a) reacting TGF- $\beta_3$ , and a receptor of a cytokine of the TGF- $\beta$  family, and a test substance, wherein the TGF- $\beta_3$ , and receptor of a cytokine of the TGF- $\beta$  family, are selected so that they bind to form a ligand-receptor complex; and

(b) comparing to a control in the absence of the substance to determine if the substance stimulates or inhibits the binding of TGF- $\beta_3$ , to the receptor and thereby regulates trophoblast invasion.

15. (Original) A method for evaluating a substance for its ability to regulate trophoblast invasion comprising the steps of:

(a) reacting TGF- $\beta_3$ , HIF-1 $\alpha$ , and a test substance, wherein the TGF- $\beta$ , and HIF-1 $\alpha$  bind to form a TGF- $\beta_3$ , - HIF-1 $\alpha$  complex; and

(b) comparing to a control in the absence of the substance to determine if the substance stimulates or inhibits the binding of TGF- $\beta_3$  to HIF-1 $\alpha$  and thereby regulates trophoblast invasion.

16. (Original) A receptor complex comprising TGF- $\beta$  R-I (ALK-I)-TGF- $\beta$  RII-endoglin.

17. (Original) A composition for regulating trophoblast invasion comprising an inhibitor of (a) TGF- $\beta_3$ , (b) receptors of cytokines of the TGF- $\beta$  family, or (c) HIF-1 $\alpha$  in an amount effective to reduce trophoblast invasion, and a carrier, diluent or excipient.

18. (Original) A composition as claimed in claim 17 wherein the inhibitor is antisense to TGF- $\beta_3$  or antisense to HIF-1 $\alpha$ .


19. (Original) A composition as claimed in claim 17 wherein the inhibitor is an antibody to TGF- $\beta_3$ .

20. (New) A method for diagnosing increased risk of preeclampsia in a subject which comprises: (a) measuring levels of placental expression of HIF-1 $\alpha$  in a sample from the subject; and (b) comparing the levels of expression of HIF-1 $\alpha$  to the levels in a subject with normal pregnancy, wherein increased levels of HIF-1 $\alpha$  compared to levels in a subject with a normal pregnancy indicates an increased risk of preeclampsia in the subject.

21. (New) A method as claimed in claim 20, wherein the levels of placental expression of HIF-1 $\alpha$  are measured by detecting, directly or indirectly, the interaction of the HIF-1 $\alpha$  in the sample with an antibody specific for the HIF-1 $\alpha$ .

22. (New) A method as claimed in claim 21, wherein the antibody is labeled with an enzyme, fluorescent, luminescent or radioactive material.

23. (New) A method as claimed in claim 21, wherein the antibody is used in counter immuno-electrophoresis, a radioimmunoassay, radioimmunoprecipitation assay, an enzyme-linked immuno-sorbent assay (ELISA), a dot blot assay, an inhibition or competition assay or a sandwich assay.

 24. (New) A method as claimed in claim 20, wherein the levels of placental expression of HIF-1 $\alpha$  are measured by detecting, directly or indirectly, the interaction of the HIF-1 $\alpha$  in the sample with a DNA molecule that binds to HIF-1 $\alpha$ .

25. (New) A method as claimed in claim 24 wherein the DNA molecule is a hypoxia inducing gene.

26. (New) A method as claimed in claim 20, wherein the levels of placental expression of HIF-1 $\alpha$  are measured by detecting nucleic acid sequences encoding HIF-1 $\alpha$ .

27. (New) A method as claimed in claim 26, wherein the nucleic acid sequences encoding HIF-1 $\alpha$  are detected using a nucleotide probe that hybridizes to the nucleic acid sequences.

28. (New) A method as claimed in claim 26, wherein the nucleic acid sequences encoding HIF-1 $\alpha$  are detected by selective amplification of the nucleic acid sequences using polymerase chain reaction.

Gr 29. (New) A method according to claim 26, wherein the nucleic acid sequences encoding HIF-1 $\alpha$  are detected by selective amplification of the nucleic acid sequences using polymerase chain reaction.

30. (New) A method according to claim 20, wherein the level of placental expression of HIF-1 $\alpha$  is measured during the first trimester of pregnancy.